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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/674,853	11/07/2000	Fulvio Mavilio	1303-110	5693

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EXAMINER	
BECKERLEG, ANNE M	
ART UNIT	PAPER NUMBER
1632	4

DATE MAILED: 03/29/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No. 09/674,853	Applicant(s) MAVILIO, FULVIO	
	Examiner Anne M Beckerleg	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *preliminary amendment filed 11/07/00* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Italy on 5/08/98. It is noted, however, that applicant has not filed a certified copy of the application as required by 35 U.S.C. 119(b).

Specification

The abstract of the disclosure is objected to because it has not been provided on a separate piece of paper. Correction is required. See MPEP § 608.01(b).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 2, 4, and 5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 recites the limitation "the *therapeutical* gene" in claim 1. There is insufficient antecedent basis for this limitation in the claim. It appears that the word "therapeutical" is a typographical error. Amendment of the claim to recite " the *therapeutic* gene" will overcome this rejection.

Claim 4 recites, "wherein said viral vector is selected from baculovirus, adeno-related viruses, adeno-virus.". Viruses are distinct from viral vectors. As such the claim are confusing. It is suggested that the claim be amendment to recite , "baculovirus vectors, adeno-related vectors, and adenovirus vectors.".

Claims 5 recites, "wherein said vector is an adenovirus". Viruses are distinct from viral vectors. As such the claim are confusing. It is suggested that the claim be amendment to recite , "adenoviral vector".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/09373, 28 March 1996, hereafter referred to as Watt et al., in view of Choi et al. (1990), PNAS, Vol. 87, 7988-7992, and further in view of Murry et al. (1995) FASEB, Vol. 9, No. 4, A883. The applicant claims methods of preparing genetically modified fibroblasts comprising ex-vivo transduction of fibroblasts with a therapeutic gene, and transformation of the cells with a high-efficiency DNA transfer method which encodes a muscle lineage commitment gene under control of a strong promoter, and fibroblasts made using said method. The applicant further claims wherein the therapeutic gene is dystrophin, wherein the muscle lineage commitment gene is myoD, and wherein the high-efficiency DNA transfer method is an adenoviral vector.

Watt et al. teaches the transduction of dermal fibroblasts which have been removed from a patient with a muscular disorder with a vector encoding dystrophin, a gene therapeutic for muscular dystrophy (Watts et al., page 6, and pages 23-24, claims 1-24). Watt et al. does not specifically teach the further modification of these cells with a viral vector encoding myoD. Choi et al. supplements Watt et al. by teaching that primary fibroblasts transduced with a retrovirus encoding myoD differentiate into striated mononucleated myoblasts and multinucleated myotubes *in vitro* which are indistinguishable from normal myoblasts (Choi et al., page 7988, abstract and materials and methods section, pages 7988-7989). Murry et al. supplements both Watt and Choi by teaching the successful transduction of fibroblasts *in vitro* with an adenovirus encoding myoD

resulting the successful conversion of the fibroblasts to skeletal muscle cells (Murry et al., abstract).

Both Watt et al. and Choi et al. provide the motivation for further transforming fibroblasts which encode dystrophin with a second viral vector encoding myoD. Watt et al. teaches that while the preferable method of treatment of muscular dystrophy would modify the patient's own myoblasts to express dystrophin, the use of myoblasts from patients with muscular dystrophy for gene therapy of MD pose several problems because the disease myoblasts have already passed through several bouts of degeneration/regeneration (Watt et al., pages 2-3, bridging paragraph). Therefore, Watt proposes using transformed fibroblasts since donor fibroblasts can fuse in vivo to make a multinucleate cell which can behave like a muscle cell (Watt et al., page 3, lines 15-22). Thus, Watt et al. provides motivation for a) transforming fibroblasts ex vivo with dystrophin, and b) utilizing cells that are capable of behaving like myoblasts for the therapy of MD. Therefore, based on the teachings of Choi et al. and Murry et al. that transduction of cells with the myoD gene results in the differentiation of the fibroblasts to actual myoblasts, it would have been *prima facie* obvious to the skilled artisan to co-express the myoD gene in the fibroblasts taught by Watt et al. in order to differentiate the dystrophin expressing fibroblasts into dystrophin expressing myoblasts for use in the therapy of muscular dystrophy. Further, based on the successful transduction of primary fibroblasts with viral vectors encoding dystrophin and myoD as taught by Watt et al., Choi et al., and Murry et al., the skilled artisan would have had a reasonable

expectation of success in preparing a modified fibroblast which has been co-transduced with both the genes for dystrophin and myoD.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Beckerleg, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Thurs and every other Friday from 9:30-7:00. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Beckerleg

A.M.S. BECKERLEG
PATENT EXAMINER